
How to Approach the Regulatory Conundrum?

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Today, farmers and the environment are benefiting from the first generation of genetically engineered (GE) crops. The biotechnology industry and academics trumpet the next generation of such crops in terms of greater nutritive value, and new sources of pharmaceuticals, antibodies, industrial enzymes, *etc.* If those crops are commercialized, is the current regulatory structure in the United States up to the task of ensuring that they are safe for humans and the environment? In this paper, I analyze the ability of the regulatory system to adequately regulate the next generation of products from agricultural biotechnology. Without additional legal authority and stronger oversight, the regulatory system cannot ensure that only GE crops that are safe for humans and the environment will be commercialized.

WHAT DOES THE FUTURE HOLD?

Virtually every week there is media coverage of new applications for agricultural biotechnology. New genes are being added to crops to make food more nutritious. For example, in the past year, the press has reported on the following potential products:

- Two genes from daffodil and one from a bacterium have been inserted into rice. “Golden” rice produces beta-carotene, which the human body converts to vitamin A.
- At University of California at Davis, scientists have transformed rice with the gene for the human breast-milk protein lactoferrin, with the objective of fighting infections.
- In Australia, a gene for a protein present in cows’ milk has been inserted into calves to enable production of higher-protein, more nutritious milk.
- Researchers are increasing the anti-oxidant properties of tomatoes by engineering them to synthesize more lycopene and increased levels of lutein (known to help fight eye disease).

Progress is being made in inducing crops to serve as “factories” for biologically active molecules in a cost-efficient and renewable manner. For example:

- Prodigene has engineered corn to produce avidin and trypsin. Avidin, naturally found in egg whites, is used in medical and biochemical diagnostics. Trypsin is an industrial enzyme used in drug production.
- Epicyte is currently engineering plants to synthesize a topically applied antibody that prevents the transmission of herpes simplex virus.
- Hirudin, a human anticoagulant protein, produced in transgenic canola, is available commercially in Canada.
- Corn has been genetically engineered to make an antigenic protein from the surface of the human immunodeficiency virus (HIV), which causes AIDS. Tests in animals are in progress for immune responses after ingestion of the transformed corn. Bananas and carrots are also being engineered to produce vaccines.

Those potential products, and many others, provide hope that the next generation of GE crops—fruits, vegetables, and grains—will benefit consumers, both in developed and developing countries, as nutritious and healthful foods and as new sources of pharmaceutical and industrial molecules.

IS THE REGULATORY STRUCTURE UP TO THE TASK OF REGULATING NEW USES OF AGRICULTURAL BIOTECHNOLOGY?

Currently, agricultural biotechnology is regulated to protect human health and the environment. Is the current federal regulatory system up to the task of thoroughly assessing how safe the next generation of GE crops will be for humans and the environment? A review of the regulatory system’s treatment of the first generation of GE crops reveals weaknesses and gaps in the current system and problems that will arise when regulating future crops. New statutory authority and stronger oversight are needed to ensure that only commercial products that are safe for humans and the environment will be marketed.¹

ENSURING THAT GE CROPS ARE SAFE TO EAT

Consumers want assurances that the foods they eat are safe. Thus, the Food and Drug Administration (FDA) should ensure the safety of biotech foods. The FDA’s current regulatory system, however, does not adequately ensure that only safe GE crops are marketed.

Current Regulation of Biotech Foods Currently, FDA does not formally approve any GE crops as safe to eat. The FDA has the authority to approve new food

¹Drugs and vaccines produced by the next generation of GE crops will be regulated similarly to their conventionally produced counterparts. Discussion of those regulatory issues is not included here.

additives, but says that the GE crops developed so far do not fall within that category. Instead, FDA has determined that GE crops are similar to conventionally bred crops and typically fall into the category of “generally recognized as safe” (GRAS) foods. FDA’s policy does allow a GE crop to be treated as a food additive requiring mandatory approval if that crop raises a food-safety concern. However, to date, FDA has not determined that any GE crop should be considered a food additive, and it is unclear if any future crop will be so considered. Both FDA and the biotech industry will strongly resist putting GE foods through the food-additive process, which is perceived as time-consuming and burdensome.

To oversee any potential food-safety concerns that might exist for a GE crop, FDA adopted a voluntary consultation process to review safety data provided by companies to ensure compliance with existing laws. In that process, the company provides summary information about the safety of its product to FDA, which, in turn, provides informal advice about the adequacy of the tests conducted by the company. In conducting its scientific safety assessment, the company provides information to show that the GE variety is “substantially equivalent”, *i.e.* as safe as its conventionally bred counterpart. To date, all commercialized GE crops have proceeded through the voluntary consultation process before marketing.

Problems with FDA Current Biotechnology Policy There are numerous problems with FDA’s current policy for GE crops. First, the consultation process is voluntary. There is no legal obligation requiring a company to provide a safety assessment to FDA and no consequences to the company that does not voluntarily consult. Second, the consultation process is developer-driven instead of FDA-driven. The biotechnology company decides what safety tests to conduct and what data to submit, because the company’s obligation is to satisfy itself that the product is safe rather than to prove safety to FDA. This process provides FDA with limited ability to require specific tests or mandate specific data. Third, FDA’s food-safety analysis is not comprehensive. Their guidance states that the consultation process is “not a comprehensive scientific review of the data generated by the developer.” Fourth, and most importantly, FDA does not determine if the product is safe. The voluntary consultation process culminates with FDA stating that it has “no further questions . . . at this time” rather than stating that the product is safe to eat.

Although no human-health problems with GE crops have been detected, the voluntary consultation process is not the most effective way to protect the consumer and engender confidence. In the coming years, the scientific safety issues raised by more-complex GE crops (nutritionally enhanced, engineered with new metabolic pathways) cannot be adequately assessed with the current industry-driven process.

FDA's Proposed Mandatory Notification Rule In January 2001, the FDA proposed regulations that would mandate notification before a GE food is marketed. Although that proposal improves upon the current process by mandating agency review and by increasing transparency, it does not change the agency's scientific review nor will it result in an official determination of safety. Under the mandatory notification, FDA still will not respond with an affirmation that the food is safe to eat. Also, if a developer markets a GE food without notifying FDA, FDA still must prove the food is adulterated before it can be removed from commerce.

How Will the Current System Treat the Second Generation of Biotech Foods?

If high-lycopene tomato makes its way to the marketplace, will FDA's current regulatory policy treat it any differently from the first generation of herbicide-resistant and pesticide-producing crops? The answer is no. It is unlikely that FDA will treat the second generation of GE crops as products that contain additives since the gene products in high-lycopene tomato or rice engineered to contain human breast-milk protein are already present in the normal human diet. Thus, the only food-safety assessment those products will receive is the less-than-comprehensive voluntary-consultation process. Those products will have to abide by the mandatory notification process, but only if FDA finalizes that proposed rule. The FDA has stated that it will not make a decision on its proposed rule before fiscal year 2003, and, if promulgated, no one knows what form the final rule will take.

A Proposal for a Mandatory Approval Process The FDA should establish a new mandatory approval process for GE crops, unrelated to the current food-additive process. It should promulgate regulations that establish testing and data requirements based on advice from a National Academy of Sciences panel charged with determining what scientific information is needed to assess food-safety concerns regarding such crops. The approval process should have time limits so that each application receives a determination within a reasonable interval. In addition, the mandatory approval process should ban any GE food with a new allergen as well as prohibit approvals for crops intended for animal feed but not human consumption. If new legislation is needed so that FDA can implement an approval process, Congress should pass such legislation.

A mandatory pre-market approval process at FDA for biotech foods would have numerous advantages over the current system. First, formal approval would provide an independent check on industry's safety determination. FDA would share responsibility for the safety determination and would help prevent food-safety mistakes. Second, it would eliminate the gap in the regulatory system that allows some biotech foods, but not others, to be marketed without pre-approval. Currently, transgenic animals require pre-market approval by FDA and pesticidal plants require pre-market approval by the Environmental

Protection Agency, yet non-pesticidal transgenic plants are subject only to FDA's voluntary consultation process. Third, a mandatory process need not be more burdensome to applicants than the current voluntary procedure. The industry states that it already conducts all reasonable and necessary tests to ensure safe products, so there is little likelihood that FDA would require significant new testing. Fourth, a mandatory approval process would make the regulatory system in the United States similar to those in Canada and Europe, where biotech foods must be affirmatively approved before marketing. Finally, a food-safety determination by FDA would go a long way to improving consumer confidence and public perception of the safety and acceptability of biotech foods. Consumers would be much more comfortable with FDA's determination that a food is safe to eat than with Monsanto or Dupont's in-house determination.

In conclusion, the benefits of a properly constructed mandatory approval process at FDA would be significant and the burden for industry need not be much greater than the current voluntary consultation process. It is unclear why industry is against a process that would provide an independent verification of a product's safety and thus sway the skeptical consumer. Therefore, producers of new GE crops should embrace sensible legislation to require a mandatory approval, such as Senator Durbin's Genetically Engineered Foods Act.

ENVIRONMENTAL ISSUES SURROUNDING GE CROPS

The second major regulatory issue for new GE crops is ensuring that they do not adversely affect the environment. For the federal regulatory system to adequately carry out that function, the system must:

- ensure that all biotech products get a thorough environmental assessment by a competent government agency before release into the environment; and
- ensure that, if products are approved with conditions to manage possible environmental risks, those conditions are adhered to (through compliance assurance and enforcement measures).

Unfortunately, the current federal regulatory system for GE crops at the United States Department of Agriculture (USDA) falls short on both accounts.²

The Current Regulatory System at USDA Under the auspices of the Plant Pest Act, the USDA has established a regulatory system for genetically engineered plants that could become plant pests. Crops subject to those regulations include (1) any crop that is a listed plant pest, and (2) any crop that has introduced DNA from a listed plant pest or an organism whose plant-pest status is

²The focus here is on the USDA regulatory process for biotech crops and not EPA's regulatory structure for plants engineered to contain a pesticide.

undetermined. For example, the regulations capture any variety that was genetically engineered using *Agrobacterium* DNA as a vector. The regulations do not include crops engineered using a gene gun, unless the inserted DNA comes from a listed plant pest or an organism whose plant-pest status is undetermined.

Any plant covered by USDA's regulation must submit to one of three oversight processes before release. The first is a notification, in which the applicant provides details about its proposed release and the USDA has thirty days to respond. The USDA has established criteria to determine which products are eligible for the notification process and guidelines that must be met to minimize environmental effects from the release. Notification is currently used to regulate virtually all of the field tests for GE crops under USDA's jurisdiction, and even for some crops that are grown commercially.

The second process is permitting, which requires a more detailed application and a longer review time at USDA before the release is authorized. Genetically engineered plants that must be permitted (instead of a notification) include crops producing pharmaceuticals and those that could affect non-target organisms. Permitting is not used as commonly as notification, although hundreds of permits have been issued since USDA began regulating GE crops.

The third process is a petition for non-regulated status. A petition is a request that USDA determine that there is no associated plant-pest risk and the crop no longer needs to be regulated. A petition for non-regulated status has been the primary pathway to commercialize GE crops. Before a petition is granted, USDA conducts an environmental assessment of the crop and seeks input through a formal public-comment period.

Inadequacies in USDA's Current System There are numerous inadequacies in USDA's current method of regulating GE crops. First, the regulatory system captures only GE crops that could become plant pests, whereas others, such as those made with the gene gun and corn DNA, do not require even a notification before release into the environment

Second, the USDA does not require a thorough environmental assessment before a regulated GE crop is released. Crops released through either the notification or the permitting process almost never receive an individual environmental assessment, yet some of those crops might have a significant impact on the environment. A recent report published by the National Research Council (NRC) stated that, "With few exceptions, the environmental risks that might accompany future novel plants cannot be predicted. Therefore, they should be evaluated on a case-by-case basis." Yet, notification and permitting do not evaluate environmental risks on a case-by-case basis since, in most cases, no environmental assessment is conducted.

Third, for those crops that do receive an environmental assessment from USDA (primarily for nonregulated status), those assessments are inadequate.

According to the NRC report: “Currently, APHIS’s³ environmental assessments focus on the simplest ecological scale. . . . APHIS should include any impact on regional farming practice or systems in its deregulation assessments.” Thus, USDA’s environmental assessments do not address all relevant environmental concerns.

Fourth, it is unclear whether USDA has the legal authority to adequately address environmental issues that arise in an environmental assessment. USDA has regulatory authority to address plant-pest risks, but does not have authority to prevent a crop’s release if it may cause ecological damage unrelated to agriculture.

Fifth, most large-scale releases occur after the GE crop has obtained nonregulated status. Although the petition process for nonregulated status is transparent, open for public comment and involving an environmental assessment, the process results in a crop that is no longer regulated by USDA. That prevents USDA from requiring post-release monitoring for environmental effects and from addressing unforeseen environmental issues. Therefore, for the vast majority of crops, USDA has extremely limited ability to address environmental issues that might arise after commercialization.

Finally, the process at USDA involves no food-safety analysis of the crop before it is released into the environment. For open-pollinated crops such as corn, a release could result in the gene-product entering the food chain. USDA’s process makes no assessment of whether that gene product would be harmful to humans if it were to enter the food supply.

Preventing Contamination of Other Crops and the Food Supply from Experimental GE Crops and/or GE Crops Producing Non-food Products When the USDA regulates a GE plant under either the notification or the permitting process, one of its goals is “to minimize persistence in the environment and inadvertent mixing with ... products which are used for food or feed.” This is accomplished, in part, by using containment and/or segregation procedures. Those procedures may limit contamination, but do not eliminate it, since eliminating all contamination is impossible.

The ability of the regulatory system to adequately contain GE plants that might harm the environment or humans is extremely important, whether it is a corn plant producing a pharmaceutical or a sunflower plant producing an industrial chemical. The USDA and FDA have stated they are working on guidelines that will address contamination issues surrounding pharmaceutical plants, but that guidance currently is not publicly available. Yet, numerous field trials and commercial planting of pharmaceutical crops have occurred without uniform standards to minimize contamination. Consumers would lose confidence in agricultural biotechnology and the safety of the food supply if

³Animal and Plant Health Inspection Service, a branch of the USDA.

they found out that some food they are eating contained a pharmaceutical or industrial chemical that has not been found safe to ingest. Thus, strong regulatory structures that minimize contamination are important.

The first way to minimize the effects of GE crops on non-GE counterparts and the food supply is through containment to limit gene flow. Containment procedures include reproductive isolation measures, such as prescribed distances for planting GE crops in areas where non-GE crops of the same species are grown, planting guard rows between GE and non-GE crops, the use of lines that shed sterile pollen, harvesting prior to flowering, netting or bagging anthers prior to pollen shed, and the staggering of flowering times with respect to adjacent crops.

For example, the USDA recently sent a letter to companies planning on planting pharmaceutical corn crops in 2002, in which distance restrictions were set forth, ranging from 0.25 to 5 miles (the latter being the distance from seed corn) and planting times for the GE corn that are either 14 or 21 days before or after adjacent non-GE corn. The letter, however, contained no scientific justification for the distances or planting times chosen nor did it state how effective the restrictions would be in reducing contamination of non-GE crops. It is unclear whether those distances and planting times will reduce the chances of gene flow by 50%, 90%, or 99%. Thus, although reproductive isolation is necessary and needs to be established, there should be a public explanation as to why certain procedures are required and what is the expected benefit.

The second type of containment procedure that minimizes persistence of the GE crop in the environment is in post-harvest activities, which includes limiting the use of land for a period of time following the crop, monitoring the land and neighboring fields for volunteer plants of the GE crop, and destroying the crop after harvest using specific procedures. Those post-harvest restrictions are important to prevent GE crops from persisting in the environment after field trials or commercial plantings. It is unclear, however, how effective they are in preventing gene transfer.

In addition to containment procedures, segregation is usually employed to ensure that experimental GE crops and those producing non-food products do not mix with crops (both GE and conventional) that are grown for food. Segregation has generally involved dedicated machinery and vehicles to harvest, transport, and store certain GE crops.

Is segregation effective in preventing contamination? When farmers planted StarLink™ corn that had been approved only for feed use, Aventis (the developer) agreed that the crop would be segregated from corn used for human consumption. StarLink™, however, ended up in the food supply, either because no segregation system was actually in place or because it was ineffective. Many experts now question whether any segregation system can effectively separate one type of corn from another. Thus, it is an open question how effective segregation can be at eliminating contamination of the food supply. If properly

set up, segregation can minimize contamination, but may never be able to eliminate it.

Enforcement When a GE crop has been approved for release, frequently the approval sets forth conditions to minimize or eliminate environmental and/or food-safety risks. It is imperative that developers and growers comply with those conditions, and it is USDA's job to verify adherence. Is the USDA doing a good job enforcing its conditional approvals? The answer is no.

The USDA has conducted some inspections of field trials and commercial releases that have permits or submitted notifications, although the level of effort is small compared to the universe of GE crops. To date, there have been over 9,000 permitted releases or notifications for GE crops, of which only a very small fraction has been inspected by USDA. The inspections USDA has conducted have resulted in approximately sixty enforcement actions, primarily letters explaining improper conduct and requesting adherence to restrictions.

When the USDA does inspect a permitted release, however, it is unclear whether those inspections are as comprehensive as needed to safeguard the environment. In particular, the USDA does not check to see if the containment or segregation procedures are working. For example, inspectors do not check neighboring fields to see if pollen has drifted to non-GE crops. Neither do they test grains on the farm or on neighboring farms to ensure that the crop has been properly segregated. Thus, the USDA should not only inspect to see if the conditions imposed on a GE crop have been met; there is need to determine whether those conditions resulted in containment and segregation.

Conclusions About USDA's Regulation of GE Crops The USDA's regulations do not adequately protect the environment or humans from current GE crops and will not adequately protect the environment and humans from the next generation of crops, such as those producing pharmaceuticals. In particular, the USDA regulatory system has the following deficiencies:

- it does not capture all GE crops;
- it does not result in a thorough environmental assessment of all GE crops;
- it does not have a mechanism for the monitoring of environmental problems that might arise after a crop has obtained nonregulated status, nor a means of enforcement if a problem occurs; and
- it does not conduct inspections to determine the effectiveness of containment procedures to minimize gene flow from GE crops or of segregation requirements to minimize food contamination from certain GE crops.

Until those deficiencies are eliminated, the federal government will not be adequately ensuring that the only GE crops released are safe to humans and the environment.

WHAT TO DO ABOUT GE CROPS THAT ARE NOT INTENDED TO BE FOOD BUT MIGHT END UP IN THE FOOD SUPPLY?

As discussed earlier, the next generation of biotech food crops will provide non-food products: pharmaceuticals, medical diagnostic proteins, *etc.* What would happen if those crops accidentally ended up in the food supply due to gene flow from pollen, contamination of seed stock, or a breakdown in an identity-preserved segregation system? Would they be safe to consume? Would they be safe to consume only at certain exposure levels? Is there any authority for FDA to review and approve those products as safe to eat in the event that they enter the food supply? Those are all questions that need to be addressed. Containment and segregation will not be 100% effective, so it is only a matter of time before one or more of the non-food GE crops enters the food chain.

The Federal Food Drug and Cosmetic Act (FFDCA) regulates everything that is intended to be used as food or feed. A pharmaceutical corn plant or a corn plant producing avidin, however, is not intended by the developer to be used as food or feed. Thus, such products are neither food additives, nor would they be subject to FDA's voluntary notification process (or their proposed mandatory notification rule). The FDA has limited authority over those products unless they show up in food. At that stage, the FDA could consider foods containing the pharmaceutical or industrial chemical as adulterated, and remove them from the market. The burden would be on FDA, however, to prove that they are adulterated.

The current system is not the best way to guarantee a safe food supply, when contamination by non-food GE crops is inevitable. A possible solution to this problem would be for the proposed mandatory FDA-approval process to apply to non-food GE crops. Under that approval system, FDA could set tolerances for non-food GE crops. Then, if that GE crop entered the food supply, eating the engineered substance would be safe as long as the amount was below the tolerance level. No consumer would need to fear that they were eating food containing unsafe substances. In addition, the rigor of the food-safety assessment conducted by FDA could be proportionate to the physical and biological confinement of the crop. If the pharmaceutical plant is grown in a location far from other corn plants, only a limited food-safety assessment might be required because the likelihood of contamination would be extremely small. On the other hand, if the pharmaceutical plant is grown in Iowa, a complete food-safety analysis might be warranted.

CONCLUSION

Although agricultural biotechnology may allow us to produce more-nutritious foods and useful medical products, the current federal regulatory structure is not up to the task of guaranteeing that they are safe. With new legal authority and better regulations, a strong, but not stifling, system can be established that independently reviews products and approves those that are safe for consumers and the environment. Such a system is essential if consumers are to have confidence in biotechnology and accept its products in the marketplace.